REMARKS

This Amendment is responsive to the Final Rejection of February 7, 2007, in which the rejection of claims 382-402 under 35 U.S.C. §112, first paragraph, was withdrawn; the objection to claims 385-388, 390, and 392 under 37 CFR 1.75(c) was withdrawn; claims 383, 384, 391, 393, and 394 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite; claim 404 was newly rejected under 35 U.S.C. §112, first paragraph, as containing new matter; and claims 382-405 were rejected under 35 U.S.C. §112, first paragraph, as lacking enablement.

New claim 406 has been presented. Antecedent basis for such claimed subject matter, which calls for growing an artery in a patient's leg, is found at pages 45, lines 1-4, and at pages 53 and 54 (Example 18) of the specification as originally filed.

Claims 383, 384, 391, 393, and 394 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner considered that the term "multifactorial and non-specific" was indefinite because the meaning of the term regarding cells is not clear. Applicant again disagrees that said claims fail to satisfy the "definiteness" requirement of the statute and submits the following remarks and evidence in rebuttal. Accordingly, favorable reconsideration of this rejection is once again requested.

It is curious that the Examiner acknowledges that the term "multifactorial" is definite when describing growth factor species, such as a protein or a gene, but yet in contrast to such acknowledgement, the Examiner considers that the meaning of "multifactorial" regarding another growth factor specie, a cell, is indefinite. If the Examiner understands and acknowledges that protein and gene growth factors may be described by the adjective "multifactorial," Applicant is at a loss to understand why the Examiner cannot understand that another growth factor, such as a cell, cannot also be described by such adjective. Certainly, one skilled in the

art, understanding that protein and gene growth factors may be described and understood to be multifactorial, would not conclude that other species of growth factors could not be likewise described. In other words, if the term is understood, and thus deemed to be definite by the Examiner in the context of proteins and genes, how could the Examiner possibly believe that such term is indefinite regarding another alternative growth factor? Once the word is understood, there should be no further question of definiteness. The Examiner has not supplied any explanation or evidence to support such selective view. The above contradictory and inconsistent position of the Examiner is further compounded by the fact that the generic term "multifactorial growth factor" is widespread in the art as evidenced by two publications cited in Exhibits A and B of the Amendment of July 27, 2006. Such term appears in the title of both publications. Hence, the Examiner must selectively ignore evidence regarding such usage and understanding of the disputed term by those skilled in the art related to the genus and two non-elected species to maintain this rejection. In view of such factual situation, it becomes the burden of the Examiner to present evidence that another specie (cells) would not be likewise understood by one skilled in the medical art. No such evidence has been presented, and thus the Examiner's position remains as unsupported opinion.

The Examiner, rather than providing evidence or a cogent explanation why cells would not be described as multifactorial despite the use of such description for growth factors, proteins, and genes, alleges that the art does not use "multifactorial and nonspecific" to describe cells. Such allegation appears to be merely a word game which attempts to change the issue rather than a *bona fide* attempt to respond to Applicant's position regarding "multifactorial." In any event, the Examiner also alleged that Applicant has bought forward no evidence to establish otherwise. Such allegation is patently incorrect as demonstrated by the evidence contained in Applicant's

Amendment of November 3, 2006. The Examiner also erroneously alleged that the term "multifactorial and nonspecific' was not used to specifically describe cells. In this regard, the Examiner's attention is directed to page 37, lines 19-22, where cells, such as stem cells and germinal cells, are described to be "multifactorial and nonspecific."

In any event, it appears to Applicant that the Examiner's professed problem in understanding the disputed terminology may be based upon a lack of appreciation that the disputed terms describe effects to be attained by growth factors, including cellular growth factors. In an attempt to assist the Examiner in understanding this medical terminology, Applicant presents the following analogy.

A substance having the potential effect to function as a catalyst is commonly referred to as a catalyst. However, such substance, prior to causing a catalytic effect for a process, does not actually perform as a catalyst. Hence, the term "catalyst" is widely known and understood to refer to a future effect of the substance. Should the substance be capable of accelerating the reaction of a given process through two or more mechanisms, the substance would properly be described to have the potential to function by a multi-mechanism effect. Should the substance be capable of accelerating the reaction of more than one process, the substance would be deemed to have the potential to be non-specific to a single process and thus not restricted to use in effecting only a single process. Likewise, the medical terms "multifactorial" and "non-specific" relate to future effects of growth factors, including cellular growth factors. By being capable of achieving a given result through the performance of more than one factor, growth factors are deemed to be multifactorial. Moreover, the ability to achieve more than one specific result renders a growth factor to be non-specific. A person skilled in the medical art would have no difficulty in understanding that the disputed terms are adjectives that refer to and describe future effects and

capabilities of growth factors, and hence such person would readily understand these terms in the context of cellular growth factors and as other types of growth factors set forth in the instant patent application. The Examiner should likewise be able to reach such understanding.

Applicant remains confounded as to why this ground of the rejection was made and maintained (for reasons that have continued to shift during the course of this prosecution, including the present Final Rejection) because such rejection is inconsistent with a prior Patent and Trademark Office (hereinafter referred to as "PTO") decision. The Examiner previously stated that it is not the policy of the PTO to perpetuate errors yet did not identify or discuss such alleged errors contained in the prior PTO determination. Rather, it appears that the respective Examiners considered Applicant's specification and claims during the course of prosecution and that the prior Examiner understood such term and the present Examiner did not. Thus, the present Examiner appears to be challenging a prior PTO determination on the basis of mere opinion that is apparently based upon a professed lack of understanding of medical terminology, rather than by presenting objective evidence. The Examiner stated in the Final Rejection of February 7, 2007 that several pieces of evidence, which were allegedly not relied upon by the prior Examiner, were relied upon in the instant rejection. However, the Examiner has not indicated what evidence was relied upon by the prior Examiner, and thus such statement amounts to mere speculation. Absent knowledge of the evidence relied upon by both Examiners, it is not possible to reach a conclusion as to the correctness of the respective determinations. Accordingly, it appears that the Examiner's challenge to the determination of the prior Examiner amounts to no more than second-guessing such determination. If such practice were to be condoned, the presumption of validity attached to an issued patent would be seriously eroded.

In connection with the above-mentioned challenge, the Examiner stated at page 4 of the prior Office Action, "When issues are first identified, they must be raised." The basis for such statement is obscure. Is the Examiner stating or implying that the prior Examiner neglected to consider whether such term is definite and understood by those skilled in the art? If so, such statement requires verification that the prior Examiner failed to consider whether or not the terms were definite. In the absence of verification, the statement appears to merely be an attempt by the current Examiner to speak on behalf of the prior Examiner and does not constitute evidence that the prior Examiner committed error. Thus, the Examiner appears to be merely substituting her opinion for that of the prior Examiner and engaging in second-guessing such prior determination.

Another important consequence of the prior Examiner's determination is that such determination, in and of itself, constitutes strong evidence that the terms are understood by those skilled in the art. When this evidence is taken in combination with the evidence presented by Applicant below, including that presented by two highly skilled physicians, there should be no doubt that one skilled in the medical art would understand such terms and that claims 383, 384, 391, 393, and 394 are definite within the meaning of the second paragraph of 35 U.S.C. §112.

It is again pointed out for the record that claims 13 and 26 of Applicant's Patent No. 5,759,033 (Exhibit A of the Amendment of November 2, 2006 and hereinafter referred to as the '033 patent) specify that the claimed growth factor is multifactorial and non-specific. The grant of these claims by the PTO constitutes compelling evidence that the disputed terms are statutorily definite.

Independent evidence supporting the prior PTO decision may be found in the results of Applicant's search, using the Google search engine, for the term "multifactorial growth factor."

Several publications were located using the questioned term to describe growth factors. In this regard, J. Biol. Chem, Vol. 280, August 5, 2005 (Exhibit A in the Amendment of June 26, 2006) relates to using the integrative nuclear fibroblast multifactorial growth factor FGFR 1. Furthermore, J. Eukaryot Microbiol, 49(5), 2002, pages 383-390 (Exhibit B in the Amendment of June 26, 2006) discloses that epidermal growth factor (EGF) is a multifactorial growth factor that activates signal transduction events in mammalian cells. Both fibroblast (FGF) and epidermal (EGF) growth factors are described as multifactorial growth factors capable of promoting the growth of soft tissue in the body of the patient on pages 20 and 21 of the specification. If such growth factor species are described by those skilled in the art as "multifactorial," then it is incumbent upon the Examiner to explain why other growth factor species, such as cells, would not also be so described and understood by those skilled in the art. Certainly, Applicant has described that growth factors can be multifactorial and non-specific (page 21 of the specification), that cell growth factors, such as stem cells, are multifactorial and non-specific (page 37 of the specification), and that gene growth factors are multifactorial and non–specific (page 50 of the specification). Unless the Examiner can provide evidence that such disclosure is erroneous, Applicant's disclosure and independent corroborative evidence must be accepted and the terms acknowledged as being definite.

Applicant once again directs the Examiner's attention to the recent *en banc* decision of the CAFC in Phillips v. AWH Corporation, 03-1269-1286, decided July 12, 2005. While the Phillips case involved patent claim infringement, Applicant believes that the principles and authorities expressed in this case are equally applicable for providing guidance to the PTO in determining the meaning of terms in the specification and claims of a pending patent application.

The Phillips decision indicated that the claims of a patent are generally given their ordinary and customary meaning in the art, citing the Vitronics v. Conceptronic, Inc., 90 F. 3d 1582 (Fed. Cir. 1996). Also cited was the Multiform Desiccants, Inc. v. Medzorn, Ltd. Decision, 133 F. 3d 1473, 1477 (Fed. Cir. 1980) for the principle that claims should be read in the context of the patent. The Court in Phillips further observed that extrinsic evidence is less significant than the intrinsic record in determining the legally operative meaning of claim language, citing C.R. Bard, Inc. v. U.S. Surgical Corp., 388 F. 3d 858, 862 (Fed. Cir. 2000). The Court in Phillips also stated that dictionary evidence can be useful in claim interpretation but that such evidence is less reliable than the patent specification and its prosecution history. Applicant submits that the Examiner should interpret the words "multifactorial" and "non-specific" in light of the specification as would be apparent to a person skilled in the medical art and thus give such words their ordinary meaning in the art to which the invention pertains. A different interpretation, such as that foisted by the Examiner, bottomed on non-contextual sources, places the term out of context and thus clearly would not be entitled to the same evidentiary weight as the interpretation by a skilled person in the medical art being appraised of Applicant's disclosure.

The Examiner purports to follow the tenants of Phillips but apparently still does not understand the disputed terms. As will be evident later, the Examiner did not follow the instructions of Phillips regarding a skilled medical person's understanding of the specification. Instead, the lack of understanding of the disputed medical terminology appears to be that of the Examiner, not of those skilled in the art. Had the Examiner appreciated, as a skilled person in the medical art would, that the specification is directed to growth factors and that a cell is a growth factor specie, an appropriate search would have indicated – and the Examiner would have become aware – that the art uses the term "multifactorial" in connection with growth factors.

This conclusion is demonstrated by Applicant's previously mentioned Google search where the genus "multifactorial growth factors" was the subject of the search. The Examiner ignored the above-mentioned disclosure of the specification (that the genus growth factors and that both the non-elected and elected species are stated to be multifactorial and non-specific) and the results of the above-mentioned Google search and relied upon a series of non-contextual searches, thereby ignoring the import of Phillips. It is clear error to ignore Applicant's generic and non-elected specie disclosure in conducting searches purporting to be conducted to a term relating to generic and specie disclosure. Such error also appears to not consider the dictates of In re Anderson, 471 F.2d 1237, 176 USPQ 331, (CCPA 1973); In re Johnson and Farnham, 558 F.2d 1008, 194 USPQ 187, 195 (CCPA 1977); and In re Fuetterer, 319 F.2d 259, 265, 138 USPQ 217, 223 CCPA 1963) where generic as well as specie related disclosure was required to be considered. These decisions make it clear that an examiner is required to consider the specification as a whole. Applicant believes that the Examiner has not so considered its specification.

The above point is underscored by the various searches performed by the Examiner and discussed in the outstanding Final Rejection. It appears that the Examiner has gone to great lengths to conduct searches in areas not related to Applicant's disclosure and has obtained results also not related to Applicant's disclosure and claims. This procedure ignores Applicant's previously presented contextual search results directed to the multifactorial growth factors disclosed in the specification. The Examiner did not explain why the results of Applicant's search were not considered to be persuasive and instead relied upon her different searches. Once again, the Examiner has ignored contextual search results of Applicant and wandered from the context of Applicant's specification. The Examiner should instead focus upon the present

invention, as described in the specification, and consider and understand the fact that a cell is a species of growth factor and then consider the highly relevant search evidence presented by Applicant.

Whether the disputed terms encompass cells other than stem cells and germinal cells is not relevant to the issue of definiteness. Rather, stem cells and germinal cells are simply examples of cells possessing such characteristics. In any event, the Examiner raised the issue as to what other types of cell may be so described. In this regard, other cell types possessing the ability to have multifactorial and non-specific effects include amniotic fluid cells and placenta "cells." Placenta cells are not true stem cells and are pluripotent, thereby illustrating the error in the Examiner's statement that all pluripotent cells are stem cells. The Examiner criticized the specification at page 5 of the Final Rejection because, "The specification does not appear to support the assertion that pluripotent cells are also considered to be part of the genus defined by "multifactorial and non-specific cells"." The Examiner's criticism is misplaced when it is considered that the specification, at page 50, indicates growth factors may be pluripotent, and at page 37, indicates that the cellular growth factors "stem cells" and "germinal cells" may be multifactorial and nonspecific.

The Examiner at pages 4 and 5 of the Final Rejection alleged that it is contradictory to consider that "multifactorial and nonspecific" cells may be both broader and more narrow than "stem" cells. There is no such contradiction because (1) not all stem cells are multifactorial and nonspecific (note unipotent stem cells) and (2) not all multifactorial and nonspecific cells are stem cells (note germinal cells). Germinal cells encompass cells that are not stem cells, as well as cells that are stem cells. For example, it is well-known that germinal cells encompass sperm cells (which are not stem cells), as well as pluripotent stem cells derived from an embryo.

Further, at pages 7 and 8 of the Final Rejection, the Examiner erroneously attempted to speak for Applicant's specification by stating that the specification implies that all stem cells are multifactorial and nonspecific and then extends such misreading of the specification by questioning why the specification did not include further wording. There is nothing in the passages to indicate that the Examiner's implied interpretation is correct. In fact, the Examiner's attention is directed to page 21, lines 14 and 15 of the specification where it is stated that, "The growth factors can be multifactorial and nonspecific." (emphasis added). Obviously, such passage does not comport with the Examiner's attempt to speak for Applicant's specification because, when the aforesaid text is read together with the passage relied upon by the Examiner, there is no reasonable basis for the Examiner's erroneous implication. To reasonably interpret Applicant's specification, the Examiner's interpretation should be factually based and consider the specification as a whole and not be based upon an alleged implication drawn from a limited portion of the specification. Furthermore, the Examiner's erroneous implied interpretation would not be so interpreted by a skilled person in the art because such person would read the specification with an understanding that unipotent stem cells, for example, are specific rather than nonspecific. It is well established in the medical art that there are stem cells which are not pluripotent. The NIH definitions (of record) indicate that there are unipotent cells (stem cells). Moreover, the Wikipedia encyclopedia (of record) evinces that the term unipotent cell, "In cell biology, is used to describe a cell (e.g. a stem cell) which has the capacity to develop/differentiate into only one type of tissue/cell type." Applicant further directs the Examiner's attention to the MJA (The Medical Journal of Australia) publication authored by Byrne et al. in 2003 entitled, "Stem Cell Therapies: A Tale of Caution" (of record) which identifies unipotent stem cells as comprising stem cells that are committed to development into

one cell type and describes attempts to reconstitute skeletal muscle as comprising a form of unipotent stem cell therapy (emphasis added). In view of the above evidence, there can be no question that the Examiner's determination that "all stem cells are at least pluripotent" is misplaced and lacks evidentiary support in this record. Accordingly, there would be no credible scientific basis for a skilled person to construe the specification in the manner implied by the Examiner.

Further, at page 5 of the Final Rejection, the Examiner continues to profess to be unfamiliar with the medical term "cascade of genetic material" because the meaning of such well-known and established medical terminology remains in question and purportedly is not understood. In response to the Examiner's questioning of the term "cascade of genetic material" and the Examiner's opinion that such language "makes no sense," Applicant previously presented the remarks set forth below.

First, such question is irrelevant to the definiteness rejection because the questioned language does not appear in the claims. Second, it is not uncommon that medical language and terminology not understood by a layman makes sense to those skilled in the medical art. Third, the questioned terminology is commonly employed in the medical art and is well understood by those skilled in the art. For example, use of the questioned terminology may be found in an article published in 2001 by the American Heart Association, entitled, "Tubes, Branches, and Pillars," authored by Hellmut G. Augustin (of record). The term "angiogenic cascade" is set forth in the first paragraph of this article. Another use of the questioned terminology may be found on website of the University of Pittsburgh, Department of Molecular Genetics and Biochemistry, regarding Nathan Bahary, M.D., Ph.D., at http://www.mgb.pitt.edu/personnnel/Bahary_Nathan.htm (of record). The term "genetic cascade" is

used in connection with vasculogenesis in the first paragraph of the second page. Clearly, if one misunderstands a basic medical term, i.e., "genetic cascade," any interpretation of "multifactorial" and "non-specific" that is based upon such misunderstanding lacks a sound foundation.

In response to the above evidence and information, the Examiner, at page 5 of the Final Rejection, stated that, "The terms "angiogenic cascade" and "genetic cascade" are NOT the same as the term "cascade of genetic material"." Is the Examiner maintaining that the terminology used in the above two publications makes sense, but the nearly identical terminology cited by Applicant does not? If such is the Examiner's position, an explanation is necessary. In any event, whether or not such terms are exactly the same, begs the question. Surely, if the Examiner can understand the terminology employed in the two publications, the term "cascade of genetic material" can likewise be understood by the Examiner. Clearly a skilled person in the medical art would reasonably understand such terms.

At page 6 of the Final Rejection, the Examiner appears to have modified her prior statements regarding the Strauer 2005 publication. In any event, the Examiner's latest comments continue to reflect a lack of understanding that multifactorial and nonspecific are adjectives that describe capabilities of cells (regenerative potential), not the cells *per se*. Once such understanding is corrected, the Examiner should have no problem in understanding Strauer's terminology and why such terminology supports the definiteness of the term "multifactorial."

As mentioned above, the Examiner attempts to support her reasoning by a lack of success in regard to search results for the term "multifactorial and non-specific cell," followed by a series of suppositions and speculations regarding the meaning of these terms. As demonstrated above, the Examiner's failed search appears to have been improperly and erroneously conducted,

ignores Applicant's search results, and certainly does not support the Examiner's position. Thus, Applicant believes that the Examiner's position amounts to no more than opinion because no meaningful objective evidence or scientifically-based explanation, such as why cells would not be multifactorial and non-specific when other growth factors are acknowledged to be multifactorial and non-specific, is presented. Had the Examiner viewed the terms "factor," "multifactorial," and "non-specific," as understood by a skilled medical person and in the context of the specification, the issue of indefiniteness would never have been raised. The meaning of the term "factor" is well known in the medical art, and one skilled in such art would have no difficulty understanding this term. Obviously, anyone understanding the medical term "factor" would also understand the term "multifactorial" to mean "more than one factor."

Applicant previously conducted a search of the NIH Medical Dictionary. The following definitions in Merriam Webster's Medline Plus Medical Dictionary (of record) were found:

Factor:	***(noun)*** A substance that functions in or promotes the function of a particular physiological process or bodily system.
Multifactorial:	***(adjective)*** Having, involving, or produced by a variety of elements or causes.

Thus, the noun "factor," as used in Applicant's specification, means a substance, such as a cell, that promotes a particular physiological process, such as the formation of a bud, and subsequent growth of soft tissue. Such definition does not describe a factor as a process, as erroneously understood and then alleged by the Examiner. "Multifactorial" is an adjective used to denote a quality of a cell. In the context of Applicant's specification, a cell is deemed to be

"multifactorial" when a variety (more than one) of elements (factors) promote the growth of soft tissue. Accordingly, there can be no doubt that the term "multifactorial" is used properly in the specification and that its meaning would be clear to one skilled in the medical art. Note again that in connection with the term multifactorial, the Examiner previously acknowledged that, "It is used to describe a cause (for example, of the disease) or an effect (for example, of the genes)." (emphasis added). However, the Examiner somehow continues to fail to understand the term despite the fact that the above underscored passage is consistent with the above definitions provided by Applicant and the disclosure at page 23 of the specification. The above-mentioned definitions are consistent with Applicant's specification; with the above-furnished materials; with the use of this term by those skilled in the medical art, such as Drs. Heuser and Lorincz; and with the previous determination of the PTO.

The questioned terms were "read and understood" by skilled persons in the art, i.e., by Dr. Heuser in his Declaration in a related application (of record) and in his Second Supplemental Declaration in a related application (of record) and by Dr. Lorincz in his Supplemental Declaration in a related application (of record) and in his Second Supplemental Declaration in a related application (of record). The Examiner previously criticized such evidence, as it pertained to Dr. Heuser's Declaration and Dr. Lorincz' Supplemental Declaration because, "they do not explain what cells are encompassed by the term." Such criticism misses the point because it is clear that the terms were read and obviously understood by these two experts in the medical art, thereby showing that the terms are, in fact, definite. It is noted that all of the above-mentioned declarations state that relevant portions of the specification regarding multifactorial and non-specific cells were "read and understood" by Drs. Heuser and Lorincz, thereby further underscoring that such terms are understood by those skilled in the medical art. Surely, the

Examiner does not contend that such experts do not understand the disputed terms. It appears that the Examiner has continued to ignore such compelling evidence from skilled persons in the medical art and instead has merely relied upon her unsubstantiated opinion.

The Examiner is again reminded that Applicant's specification indicates that multifactorial and non-specific cells may include stem cells and germinal cells. The Examiner has concocted an issue that other cells are not mentioned. Initially, the Examiner erroneously raised the issue that only stem cells were included. Upon Applicant pointing out that germinal cells were also included in the specification, the Examiner then changed the purported issue to what further cell types were included. Applicant believes that the disclosure of the above-mentioned two types of multifactorial and non-specific cells, along with the identification of such well known cells as pluripotent, amniotic fluid, placenta, and bone marrow stem cells, is fully adequate to describe examples of types of cells having the described characteristics to one skilled in the art. Applicant points out further that the number of types of cells that may be multifactorial and non-specific is not relevant to the understanding and definiteness of these disputed terms and thus the disclosure of stem and germinal cells is adequate.

Another example supporting the definiteness of the questioned terms by workers skilled in the medical art that is consistent with the description in Applicant's specification, the definition of "multifactorial," the above-mentioned NIH Medical Dictionary, and Drs. Heuser and Lorincz, is be found in Strauer 2005 (of record). Dr. Strauer states at page 1656, second column, third paragraph that, "The regenerative potential of bone-marrow-derived stem cells may be explained by any of four mechanisms." These four-cell biologic and molecular mechanisms are further described as "factors" at page 1657, second column, second full paragraph. Therefore, it is clear to a skilled person in the medical art that Dr. Strauer and his co-

authors identify the regenerative potential of bone marrow stem cells as being derived from at least four different mechanisms/factors or characteristics of such cells. It follows that bone marrow stem cells can be appropriately styled as four-factor cells, i.e., multifactorial. Thus, Strauer 2005 confirms that yet another skilled group of medical experts possesses an understanding of "multifactorial" cells that is consistent with that of Applicant, the evidentiary materials discussed herein, and the prior PTO determination.

In the prior Office Action at page 9, the Examiner acknowledged that, "Even if Strauer 2005 could be tortuously construed as describing bone marrow stem cells as multifactorial, Strauer 2005 only discusses bone marrow stem cells" (emphasis added). Whether or not Strauer 2005 only describes bone marrow stem cells is beside the point because such publication discloses the term "multifactorial" in a definite, understandable manner with reference to cells. Note further that Applicant describes using the same stem cells as Strauer 2005–bone marrow stem cells. Whether characterized as tortuous or being clearly evident to one skilled in the medical art, the fact remains that Strauer 2005 fairly and reasonably teaches that a type of stem cells are multifactorial and thus supports Applicant's position. It would seem to Applicant that the Examiner's acknowledgement in the above quoted passage should serve to conclusively resolve this issue. Also at page 6 of the present Final Rejection, the Examiner stated that, "Strauer 2005 uses 'four mechanisms' to describe regenerative potential," not the cells *per se*. Thus a skilled person in the art would readily recognize that the bone marrow stem cells of Strauer 2005 are multifactorial.

For the record, the Examiner's attention is again directed to yet another publication in which a skilled medical person utilizes the term "multifactorial" in a manner consistent with Applicant's specification; namely, the 2001 publication of Caplan et al. (Exhibit E of the

Amendment of June 26, 2006 and hereinafter "Caplan 2001") entitled, "Mesenchymal stem cells: building blocks for molecular medicine in the 21st century." Note the use of the term "multifactorial" in this publication. Caplan 2001 teaches that mesenchymal stem cells prevalent in bone marrow are pluripotent in that they are capable of differentiating into multiple tissues types. Caplan 2001 further teaches that such bone marrow stem cells undergo multifactorial differentiation pathway from stem cells to functional tissues including elaborate composite tissues *in situ*. This description is consistent with Applicant's use of the terms "multifactorial" and "non-specific" to define pluripotent cells such as bone marrow stem cells and germinal cells, which induce or promote the growth of composite soft tissues. The Examiner previously took issue with Caplan 2001 by stating that this publication describes a process. Such position is clearly erroneous and ignores the above-presented definition of a factor.

An earlier publication of Caplan; namely, a publication entitled, "Mesenchymal Stem Cells," Journal of Orthopaedic Research, Volume 9, No. 5, 1991, pages 641-650 (cited in the Sixth Supplemental Information Disclosure and hereinafter "Caplan 1991"), describes bone marrow stem cells as exhibiting multifactorial characteristics. Accordingly, Applicant believes that Caplan 1991, like Caplan 2001, contains compelling evidence that those skilled in the medical art understand and use the questioned terms in a manner consistent with Applicant's use thereof. Caplan 1991 described mesenchymal stem cells ("MSC"), which were harvested from bone marrow and/or periosteum, as comprising multifactorial cells. Specific passages of Caplan 1991 are referenced below in support of Applicant's position.

Regarding Applicant's use of the term "multifactorial cells," which cells are species of the described and claimed genus "growth factor," Caplan 1991 recognized and attributed

multifactorial characteristics to MSC at page 641, left column paragraph 1, lines 8-14 and at the top of page summary, lines 6-8.

The first reference at page 641 is as follows:

> Their progeny are affected by a number of factors, however, as they become tracked into very specific developmental pathways in which both intrinsic and extrinsic factors combine to control the molecular and cellular pattern of expression that results in specific tissues that perform specific functions based on their molecular repertoire (9,11).

The second reference at page 641 is as follows:

> Local cuing (extrinsic factors) and the genomic potential (intrinsic factors) interact at each lineage step to control the rate and characteristic phenotype of the cells of the emerging tissue.

As would be understood by a skilled person in the medical art, Caplan 1991 clearly characterizes MSC as multifactorial cells because more than one factor is described; and thus no issue regarding the meaning of "multifactorial" should remain.

Applicant's search also revealed the Merck Manual of Geriatrics, Ch. 72, Cancer (Exhibit F of the Amendment of June 26, 2006) which describes "Oprelvekin, a nonspecific growth factor for megakaryocytes" and the NIH Pub Med abstract identifying "Erythropoietin as a nonspecific growth factor and its effect on carcionogenesis" (of record). Regarding the limitation "non-specific" cells, species of the genus "growth factor," Caplan 1991 disclosed that MSC are lineage-nonspecific, i.e., they can develop into nine (9) separate and unique tissues. In this regard, see Fig.1, page 642. Thus, it is patently clear that a person skilled in the art understands the meaning of the term "non-specific" when applied to cells, such as stem cells – they are lineage-nonspecific and can develop into a variety of tissues. The Examiner stated that these

publications do not address the question of the meaning of multifactorial and non-specific. To the contrary, the publications in fact demonstrate such definitions. For the Examiner to deny this fact requires a denial of pure science, and there can be no further issue regarding the understanding of such term by one skilled in the medical art.

It is submitted that Applicant's above-mentioned evidence, when considered with the authoritative statements and precedential tenets of Phillips, Anderson, Johnson and Farnham, and Fuetterer must be accorded far greater evidentiary weight than the Examiner's unsubstantiated speculation as to the intended meaning of the questioned term. When following these decisions and thus reading the claim language within the complete context of the specification with the understanding of a person skilled in the medical art, Applicant believes that there can be no question as to the meaning of "multifactorial." The meaning of "non-specific" as being synonymous with "non-specialized" is apparent from previous submissions and the above-mentioned evidence.

When it is considered that the PTO previously determined – and obviously believed – that the questioned terms are definite, that Drs. Heuser and Lorincz read and understood such terminology, and that Applicant presented a large body of independent evidence supporting, and consistent with, the prior determination of the PTO and Applicant's medical experts, it appears that the Examiner is the only one that does not understand such terms. Surely, the Examiner's opinion and stated lack of understanding of such medical terminology cannot overcome such compelling evidence. Accordingly, this aspect of the indefiniteness rejection should be withdrawn. The Examiner's conclusion that "...in view of the preponderance of the totality of the evidence, the rejection is maintained." is contrary to the extensive evidence of record and is without merit.

In summary, Applicant believes that once the Examiner's misunderstanding of the questioned terminology is transformed into an understanding consistent with that used by a skilled person in the medical art, there should be no further issue remaining. Applicant submits for all of the above reasons that claims 383, 384, 391, 393, and 394 are in compliance with the definiteness requirement of the statute and that the Examiner's rejection should be withdrawn.

Claim 404 stands rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner posits that newly added claim 404 contains subject matter that is unsupported in the specification as originally filed. Applicant disagrees with such rejection for the following reasons.

Specifically, the Examiner states that the specification as originally filed does not provide antecedent support for "administration to a damaged site in a leg of a patient." Applicant disagrees. Example 18 provides support for intramuscular administration of a growth factor to a damaged artery in the leg of a human patient. The Examiner's statement that, "a damaged artery in a leg is not the same scope as damaged site in a leg" is inept at best. The real issue is not whether the language "damaged site" is specifically recited in Example 18 but whether the concept of administrating a growth factor to a damaged site in the body, e.g. leg or heart, is conveyed by the original disclosure considered as a whole. See In re Anderson, supra. and In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981). The specification as filed is replete with disclosure relating to the concept of administering growth factors to a "desired site" in the body for promoting the growth of soft tissue, such as an artery, as exemplified on page 45 and in Example 18 of the specification.

Further, the Applicant disagrees with the Examiner's statement that "the specification does not envision administration of cells at the damaged artery." The written description

requirement of the statute "serves to insure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material." In re Wertheim, 541 F.2d 257,262, 191 USPQ 90, 96 (CCPA 1976). The Court in In re Alton, 76 F.3d 1168, 37 USPQ 1578 (Fed. Cir. 1996) held that an applicant in satisfying the written description requirement:

> "...does not have to utilize any particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.' In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citation omitted). Put another way, 'the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.' Vas-Cath, 935 F.2d at 1563-64, 19 USPQ2d at 1117. Finally, we have stated that '[p]recisely how close the original description must come to comply with the description requirement of section 112 must be determined on a case-by-case basis.' Eiselstein v. Frank, 52 F.3d 1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (quoting Vas-Cath, 935 F.2d at 1561, 19 USPQ2d at 1116)."

It is trite law that the entire disclosure must be considered by the Examiner when determining compliance with the description requirement of the statute, see In re Anderson, supra. The Examiner has failed to explain wherein the rejected claims in calling for cellular growth factors define subject matter completely outside the scope of the specification. The specification clearly contains a description of the claimed invention using descriptive words that fully set forth the claimed subject matter, albeit not *in haec verba.* See Eiselstein v. Frank, 52 F.3d 1035, 1038, 34 USPQ 2d 1467, 1470 (Fed. Cir. 1995). All the limitations of claim 404 appear in the specification. The specification is replete with description of inserting a growth factor for promoting soft tissue growth at a desired (damaged) site in the body (pages 20, 21, 32,

45, 52, 53, 56, and 62). Appropriate growth factors within the scope of Applicant's invention are described as comprising living organisms (page 20), such as cells (page 37), or a patient's own cells (pages 47 and 48) and particularly stem cells (pages 37, 40, 41, 42, 46, 48, 51 etc.) such as bone marrow stem cells (bone marrow mononuclear cells/BMCs) and germinal cells. One skilled in the art reading the subject application would understand that Applicant's invention is not limited to using a particular growth factor, such as the cDNA clones specifically described in Example 18 but, rather, includes the use of a broad class of described growth factors, including cells, such as stem cells. Claim 404 is directed to an alternative embodiment to the growth factor of Example 18. One skilled in the art reading the subject specification would readily understand that, as of the filing date, applicant was in possession of the claimed invention. There can be no doubt that under current law the specification satisfies the description requirement of the statute by containing an equivalent description of the subject matter of claim 404.

Claims 382-405 were rejected under 35 U.S.C. §112, first paragraph, as failing to satisfy the enablement requirement. Specifically, the Examiner on page 9 of the Final Rejection stated that:

> The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant disagrees that the scope of protection provided by the appealed claims is not adequately enabled by the application disclosure under current law.

At the outset, Applicant believes that there are three important factors to consider when determining whether the instant specification contains a disclosure that would have enabled a

skilled person in the medical art to make and use the claimed invention. When these factors are considered, there can be no doubt that Applicant's specification provides an enabling disclosure. The three factors are discussed below.

First, there is a considerable body of disclosure provided by the subject application relating to Applicant's generic invention of promoting the growth of soft or hard tissue in human patients, including growing a new artery, by administering a broad class of growth factors including cellular growth factors such as stem cells suitable for effecting such tissue growth. In this regard, Applicant's specification (pages 20, 21, 30-32, and 38-42) provides a substantial body of disclosure regarding using a growth factor to form a bud and grow soft tissue in a human body. The specification (pages 20, 21, 31, 32, and 37- 52), describes a class of growth factors that broadly and specifically includes genes, nucleic acids, a patient's own cells (autologous cells), or universal cells, e.g., stem cells (mononuclear bone marrow cells), etc., all of which are described to promote tissue growth through differentiation and morphogenesis. The Examiner has only considered the disclosure regarding enablement as it specifically relates to the elected growth factor species, cells, and to unclaimed administration modes and apparatus. The Examiner's selective reading, which ignores Applicant's broad and specific disclosure relating to non-elected growth factor species disclosure, is clearly erroneous under current law. When an applicant elects to prosecute a species following an election requirement, the Examiner is not permitted to wear blinders and focus solely upon the elected species and ignore the scope of enablement provided by the specification as a whole, which includes the genus and non-elected species. There should be no doubt that the specification taken as a whole, when properly read and understood by one skilled in the art, meets the statutory requirement for enablement under current law.

Second, the Examiner has not taken issue, nor can issue be taken, with the fact that the administration techniques and administered materials disclosed by Applicant were individually old and well known as of the filing date of the instant patent application. The February 13, 2001 Declaration of Dr. G. Robert Meger (of record) demonstrates that the administration techniques and administered materials used in practicing the invention were known at the filing date of the application. The materials and administration techniques disclosed by Applicant were routinely employed in the medical art, but not in the claimed combination, at the time the instant application was filed.

Third, the Examiner has admitted that the level of skill in the art is high. Applicant agrees that the skill level is high when it is considered that many years of education, training, and experience are required in the medical field. The instant specification is addressed to and is understood by such highly skilled and trained persons.

Once the above-identified relevant materials and administration techniques set forth in the subject specification are properly considered in their entirety, Applicant believes that there should be no question that one skilled in the medical art is enabled to make and use the claimed invention. This conclusion is reinforced, as noted above, by the fact that the materials and administration techniques, but not the inventive results, were well known when the instant application was filed. MPEP Section 2164 states that the purpose of the enablement requirement is to describe the claimed invention in such terms to permit one skilled in the art to make and use the invention. Such Section cautions that detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention. MPEP Section 2164.01 states that:

> A patent need not teach, and preferably omits, what is well known

> in the art. *In re Buchner*, 929 F2d. 660, 661, 18 USPQ 2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d. 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) cert denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F2d. 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Applicant believes that the above caution is especially relevant to the instant factual situation where the Examiner has conceded that there was a high level of skill in the art at the time the instant application was filed and, coupled with the unchallenged evidence contained in Dr. Meger's Declaration, that all the materials, methods, and apparatus needed to practice the invention were well known at the time of the invention. Thus, Applicant submits that the instant disclosure clearly enables one skilled in the medical arts to make and/or use the full scope of the claimed invention without undue experimentation because a reasonable consideration of the three above-delineated factors and the interaction thereof leads to the inevitable conclusion that the disclosure is enabling.

The Examiner has the burden to establish and support by convincing objective evidence a *prima facie* case of lack of enablement. For reasons set forth below, Applicant believes the Examiner has failed to meet such burden.

The first paragraph of the statue requires nothing more than objective enablement, and it is of no importance whether such teaching is set forth by use of illustrative examples or by broad terminology. As a general matter, an application's disclosure, which contains a teaching of how to make and use the invention in terms which correspond in scope to those used in describing the invention sought to be patented, is considered to be in compliance with the enabling requirement of the statue. In re Marzocchi, 439 F.2d 220, 169 USPQ 367, 369-370 (CCPA, 1971). Further, "Section 112 does not require that a specification convince persons skilled in the art that the

assertions therein are correct." [Emphasis added]. In re Robins, 429 F.2d 452, 166 USPQ 552 (CCPA, 1970).

When evaluating enablement, it is incumbent upon the Examiner to determine what subject matter each claim recites, i.e., the scope of protection sought for each claim. The scope of dependent claims are properly determined with respect to 35 U.S.C. §112, fourth paragraph. See MPEP Section 2164.08. The Examiner has taken the position that more than routine experimentation would be required to practice the claimed invention and addresses this issue by reference to the guidelines established in In re Wands, 858 F.2d 731, 737, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988). As evidence in support of the non-enablement determination, the Examiner relies on the Strauer et al. publication (hereinafter "Strauer"). Strauer does not reasonably relate to intramuscular injection of stem cells into a human patient's heart or leg and growing an artery as required by claims 395, 396, 398, 399, 402, 403, 404, 405, and 406. Thus, Strauer cannot reasonably be said to be relevant to the enablement of the claims in issue.

Initially, Applicant points out that it is evident the Examiner failed to consider the disclosure provided by the subject specification as a whole in determining compliance with the enablement requirement of the statute. The appropriate factual determination is whether the instant specification reasonably directs one skilled in the art how to make and use the claimed subject matter. As demonstrated above, the Examiner erroneously restricted the factual determination to the elected species of growth factor and, thusly, ignored those portions of the specification describing a broader generic invention and also ignored disclosure related to non-elected species. Applicant is entitled to have the entire disclosure considered in determining compliance with 35 U.S.C. §112, first paragraph. See In re Anderson, supra. and In re Johnson and Farnham, supra. Further, it is well settled that the test for enablement must take into

consideration that which is known in the prior art – that a patent should preferably omit that which is well known/understood in the particular art to which the claims are directed. See MPEP Section 2164.01 and the authorities cited therein.

Applicant submits that a careful analysis of the Wands factors in light of the application disclosure compels a conclusion that undue experimentation would not be required to practice the claimed invention. Contrary to the Examiner's assertion, the Strauer publication does not disclose any experimental protocol required for practicing the invention. Rather, Strauer discloses following protocols that were routinely used in the art and employed an off-the-shelf angioplasty balloon catheter, such as, for example, a catheter of the type described in Nabel et al. U.S. Patent No. 5,328,470 (of record), for transplanting autologous bone marrow mononuclear cells to treat acute myocardial infarction (MI) in human patients. The Examiner has not critically reviewed the enablement provided by Applicant's disclosure *vis-à-vis* the scope of the rejected claims. Strauer does not describe using any experimental protocol to determine appropriate cell population, i.e., there is no requirement for using specific bone marrow stem cell species. Strauer uses the selfsame bone marrow mononuclear cells (BMC's) disclosed by Applicant. Regarding time of treatment, Strauer does not disclose that determining time of treatment required experimentation. Strauer (published in 2002) elected to treat patients following five to nine days after suffering an MI. Note that a later publication of Strauer, the 2005 Strauer publication (of record), discloses treating chronic MI in patients that had transmural MI some 27 months earlier. Again, no experimentation regarding treatment time was noted. It is evident that the time of treatment following an MI is not a critical variable and undue experimentation would not be required. Applicant points out that Strauer 2005 is the "best evidence" in regard to whether time of treatment in human patients is critical. Strauer 2005 teaches that stem cells can

be used to successfully treat MI in human patients suffering either acute or chronic disease. Thus, the Examiner's conclusion that "great quantities of experimentation" would be required to practice the claimed invention is mere opinion, is not supported on the record, and is fatally flawed. It is apparent from the record that no more than common sense would be required to determine time of treatment because Strauer has demonstrated that timing is not a critical parameter.

The Examiner's contention that the details for treating a patient worked out by Strauer "involved the act of invention" is misplaced. None of the rejected claims require the use of an angioplasty balloon catheter; and, therefore, it is improper for the Examiner to look solely to Strauer for guidance. Secondly, application Examples 18, 19, and 36 describe a detailed regimen for treating a patient with a damaged heart (19 and 36) or leg (18) by injecting a growth factor for promoting artery growth, which includes mode, dosage, and means for evaluating success of treatment. Specifically, Example 18 (page 53, line 25 to page 54, line 4) describes a regimen wherein cells are injected slowly and which employs a containment system to prolong cell contact time and to avoid leakage or wash away of cells. The application disclosure also teaches on pages 40-42, 47, and 48 utilizing autologous cells, i.e., stem cells, harvested from bone marrow (BMC's) and blood of the patient (self-cell therapy) or from cell cultures (allogenic) to grow organs, i.e., arteries, by differentiation and morphogenesis (page 48). That Strauer fails to report formation of a bud is irrelevant. The relevant issue is whether Applicant's specification is enabling in regard to the claimed subject matter, which calls for forming a bud and growing a desired soft tissue, such as an artery. The specification at pages 20, 21, and 30-32 clearly enables the claimed invention by teaching injecting a growth factor into a patient's body at a selected location to form a bud and growing a desired hard or soft tissue in said body (see also

pages 38-42). Thus, whether or not Strauer's publications involve the act of invention is not relevant.

The Examiner states that, "The specification contains only prophetic Examples," but fails to explain how this fact supports a holding of non-enablement and, for good reason, since actual working examples are not a requisite for satisfying the enabling requirement of the statute and prophetic examples are specifically sanctioned by the PTO. Actual working examples are not required if the invention is disclosed in a manner that one skilled in the art would be able to practice it. Section 2164.02 of the MPEP states that:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

The Examiner's contention that, "None of the prophetic examples are directed to administration of cells to form a bud and then grow soft tissue" is inept and ignores the specification and record as a whole. One skilled in the art reading the specification at page 20, 21 and 30-32 would understand that Applicant's invention included injecting a growth factor to form a bud and cause growth of desired soft tissue, such as an artery (organ). Further, one skilled in the art reading the application at page 46, lines 3-8 would readily understand that Applicant disclosed a method comprising seeding, e.g., injecting, appropriate cells (stem cells) or other growth factors to promote growth of blood vessels (arteries) in a damaged portion of a human heart or leg (pages 53, 54). Moreover, one reasonably skilled in the art would understand from page 47, line 22 through page 48, line 15 that a patient's own (autologous) stem cells can

be used to grow function specific tissue, such as an artery, through differentiation and morphogenesis. Those skilled in the art understand that "morphogenesis" is the formation and differentiation of tissues and organs and that an artery is an organ. See pages 33 and 48 of the specification. Examples 1-17 of the specification teach the formation of a tooth, eye or kidney, all of which include an artery, grown from a "germ" (bud, i.e., primordium). Examples 15 and 16 describe using mononuclear bone marrow stem cells to promote growth of a kidney or eye through differentiation during morphogenesis.

Applicant agrees with the Examiner that the medical arts in general are complex. However, while the physiological reactions involved may be complex, the practice of the claimed invention is straightforward. The called-for cells, e.g., stem cells, the methods of administering, and the particular apparatus required for administering the cells are old and well known in the medical art.

The Examiner's statement at page 11 of the Final Rejection that:

> The state of the art does not support the claims' requirement that administration of cells can cause a bud to be formed and tissue consisting of desired soft tissue to be grown and integrated into the patient's body. Publications disclosing administration of cellular material (blood transfusions, organ transplants, etc.) can be found. However, no publications regarding formation of a "bud" which grows into only soft tissue can be found. It is noted that the publications and declarations of record in the instant application have been reviewed regarding this issue and also were not found to support formation of a bud which grows into only soft tissue.

Such statement evinces a total misunderstanding on the part of the Examiner in regard to the manner in which the Court applied "the state of the art" factor in In re Wands. Simply put, if the prior art had taught Applicant's invention, the parties would not be at this point in the instant

prosecution. As evidenced by the Examiner's failure to reject the claims on prior art, this is not the situation at hand.

It is beyond doubt that a skilled person in the medical art is aware that organs, such as an artery, are formed from a bud. It is also beyond doubt that arteries consist of soft tissue. Thus, the Examiner's statement that, "The publications and declarations of record in the instant application have been reviewed regarding this issue and also were not found to support formation of a bud which grows into only soft tissue," is not credible due to a lack of sound scientific basis. As pointed out in Applicant's specification at page 20, hard or soft tissue may be formed. One only has to read Paragraph 5 of the respective Declarations of Drs. C. Gene Wheeler, Wayne H. Finley, and Andrew E. Lorincz (all of record) to understand that a bud is a primordium for the formation of soft tissue, such as an artery. Moreover, the article entitled, "VNS CLOSURE using the method we developed at the Whiteley Clinic," posted February 26, 2007 on the Whiteley Clinic website, http://www.varicost-vein.co.uk (attached hereto as Exhibit A) confirms the above-mentioned statements at Paragraph 5 of the Declarations.

As demonstrated above, the Examiner's statement regarding Applicant's declaration evidence is inept, at best, and does not fully address such evidence. Specifically, the Examiner failed to address Paragraphs 3-7 of the three above-mentioned Declarations. Of particular note is Paragraph 7, wherein each Declarant opines that, "The process of placing a growth factor at a desired site of a human body will produce a bud that will predictably subsequently grow into soft tissue...," as described in the subject application. Clearly, those skilled in the art understand that a bud is an organ primordium, as evidenced by Paragraph 5 of each of the three above-mentioned Declarations.

Applicant is the first to teach injecting growth factors, including cells, such as stem cells, in the body of a human patient to grow *in vivo* soft tissue, such as an artery. This is Applicant's contribution to the medical art. The Court applied this factor in determining whether all the materials and methods needed to practice the Wands invention were known in the art. Applicant relies upon the instant specification and not upon any "post-filing date publications" to support enablement of the claimed subject matter.

The Examiner admits that the level of skill in the art was high at the time the instant application was filed.

The Examiner states that the claimed invention is unpredictable because of its use of physiological agents, citing supporting authority. However, the Examiner does not provide any succinct reasoning or evidence as to why one skilled in the art would doubt that the asserted scope of objective enablement in Applicant's specification is not in fact commensurate with the scope of the claims. Accordingly, the Examiner's statement is based upon opinion, not objective evidence. The specification provides multiple embodiments using multiple well-known species of growth factors for promoting artery growth employing multiple well-known administration modes carried out with multiple well-known apparatus.

The Examiner states at page 12, first paragraph, of the Final Rejection that, "The breadth of the claims is quite large." The claims are generally directed to methods for producing and integrating tissue consisting of desired soft tissue at a selected site in a body of a human patient comprising placing cells in said body of said human patient, forming a bud, and growing said soft tissue.

Firstly, the claims in issue require cells, such as pluripotent cells and stem cells, including bone marrow mononuclear cells (stem cells) and germinal cells. One of ordinary skill in the art

appraised of the specification disclosure would readily comprehend the type of cell, i.e., stem cell, required for promoting morphogenesis, e.g., artery growth. Secondly, claims 385, 386, 388, 390, 392, 400, 401 and 403-406, require forming a new artery which limits the desired soft tissue and claims 404-406 limit the location of artery growth. Examples 18, 19 and 36 describe dosages, mode of administration (intramuscular injection) of alternative growth factor (cDNA clones) and using readily available commercial devices to assess blood flow through the new artery to determine the success of artery growth. The Examiner has failed to establish why one skilled in the art would not be able to extrapolate those examples across the entire scope of the claims including the use of cells, i.e., stem cells as the growth factor. See MPEP Section 2164.02. Again, the Examiner's conclusion is based upon opinion, not objective evidence.

There is no requirement that an applicant's claims set forth the practical limits of operation for the invention. One must look to the specification, not the claims, in determining compliance with the first paragraph of the statute. It is clear that the Examiner, in determining compliance with the enablement requirement of the statute, has ignored the scope of enablement provided by the specification as a whole. The Examiner's limited evaluation of Applicant's specification constitutes reversible error. See In re Johnson and Farnham, supra., and In re Fuetterer, supra., cited therein. Moreover, the Examiner's rejection fails to specifically address the inventions of claims 402-405 requiring locally placing, i.e., injecting, stem cells into the patient's heart or leg and growing an artery.

To the extent the Examiner may be challenging the predictability of Applicant's described artery growth, both Strauer and the Perin et al. publication (hereinafter "Perin" and of record), which describe implanting mononuclear BMC's to provide blood vessel regeneration and attendant heart repair, suffice to ally such challenge. Perin, in particular, provides autopsy

proof that BMC's promote neovascularization, i.e., artery growth, which is consistent with claimed new artery growth. Regarding "prior art," none has been identified or cited by the Examiner against Applicant's claims and for good reason. Applicant was the first to disclose and claim a method for treating human patients by implanting cells, such as stem cells (eg., bone marrow mononuclear cells or BMCs), in the body and growing a new artery.

It is a fact that the disclosed administration techniques were well established in the medical art prior to Applicant's invention and must be considered in any evaluation of enablement. It is also a fact that cells, including stem cells, were well known and characterized prior to Applicant's claimed invention. The Examiner is respectfully requested to take Official Notice of the fact that processing bone marrow and peripheral blood for recovering mononuclear stem cells was routine in the medical art prior to Applicant's invention. Typically, bone marrow transplant procedures involved removing bone marrow from the patient which is filtered, treated, and transplanted immediately or frozen and stored for later use. Another established fact—that stem cell banks were created as early as the 1950's–indicates that those skilled in the medical art were familiar with harvesting, handling, culturing, preserving, separating, and storing, etc. such stem cells. The handling and treatment of cells, as well as stem cells, has been long known and practiced in the medical art prior to Applicant's filing date. In this regard, see the Trigg 2002 publication in Pediatric Transplantation entitled, "Milestones in the Development of Pediatric Hematopoietic Stem Cell transplantation – 50 Years of Progress" (of record). As mentioned in this publication, stem cell handling and preparation techniques have been known for decades. The publication provides evidence of the fact that stem cells harvested from bone marrow and from blood of patients has long been known and isolated as part of national blood bank programs. Further, the Examiner is referred to three publications (all of record); namely: (1)

Areman, et al. 1990 publication in Prog. Clin. Biol. Res., entitled, "Automated Isolation of Mononuclear cells using the Fenwal CS3000 blood cell separator;" (2) Angelini, et al. 1990 publication in Haematologica, entitled, "Human bone marrow processing using Cobe 2991 and CS 3000 blood cell separators for further ex vivo manipulation;" and (3) Janssen, et al. 1992 publication in J Hematother, entitled, "Use of the Terumo SteriCell for the processing of bone marrow and peripheral blood stem cells," which confirm the above-mentioned facts. In addition, the Caplan 1991 publication in Journal of Orthopaedic Research entitled, "Mesenchymal Stem Cells" (cited in the Sixth Supplemental Information Disclosure and hereinafter "Caplan 1991" and of record) reported culturing human bone marrow and isolating mesenchymal stem cells for growing bone in murine models. Applicant believes that such evidence confirms the fact that cells, including stem cells, were well known and characterized in the medical arts prior to Applicant's claimed invention. One reasonably skilled in the art appraised of such knowledge when viewing applicant's specification disclosure would readily be able to predict and comprehend that stem cell growth factors are equivalent to cDNA clones described in Example 18 for providing the desired artery formation.

Once the relevant materials and administration techniques set forth in Applicant's specification are properly considered in their entirety, Applicant believes that there should be no question that one skilled in the medical art is enabled to make and use the claimed invention. This conclusion is reinforced by the fact that the materials and administration techniques, but not the inventive result, were well known when the instant application was filed. Thus, Applicant submits that the Examiner has apparently failed to comprehend that Applicant has used old and routine administration techniques and old materials to achieve a remarkable new result: growth of soft tissue, i.e., an artery, in the body of a human patient. Inasmuch as the claimed

administration techniques and materials were well known to those skilled in the art, a person skilled in the medical art would not require an extensive, detailed description of such old elements of the invention and thus would be enabled to make and use the claimed invention once guided and directed to the administration techniques and materials by Applicant's specification. It is noted that the Examiner has not challenged the fact that these elements were known as of the filing date of the instant application, and for good reason.

In summary, Applicant believes that the Examiner's evidence of lack of enablement, which comprises the Examiner's erroneous assessment of Strauer as discussed above, when considered *vis-à-vis* the evidence of enablement provided by Applicant's specification combined with a fair and reasonable reading of Strauer fails to establish a *prima facie* case of lack of enablement under current law. It has been further demonstrated above that the Examiner's conclusion is not supported by sound, objective evidence. Rather, the conclusion is speculative and thereby amounts to no more than the Examiner's opinion. Thus, this rejection should be reversed.

Assuming, *arguendo*, that the Examiner somehow met the burden of establishing a *prima facie* case of lack of enablement, Applicant believes that any such case has been rebutted by the submission of the multiple Declarations of experts in the field, Drs. Wheeler, Finley, Meger, Lorincz, and Heuser (all of record). Please note that additional Third Supplemental Declarations of Dr. Lorincz and Dr. Heuser are being filed concurrently with the instant Amendment, and are attached hereto as Exhibits B and C. The conclusions set forth in the respective Declarations establish an objective fact that is highly material to a determination of enablement. These highly skilled medical experts read relevant portions, including generic and non-elected species portions, and reached the determination that one skilled in the medical arts, armed with the

knowledge in the disclosures, would be enabled to practice the claimed method and to predictably anticipate the results defined therein without need for resorting to undue experimentation.

The Examiner attempted to diminish the weight to be accorded to such Declarations by erroneously stating that the, "Declarations of record...were not found to support formation of a bud which grows only into soft tissue." As pointed out earlier, there is a clear nexus between the claims and the declaration evidence. Other than restating her opinion, the Examiner has not met her burden of addressing the probative value of the objective evidence in Applicant's Declarations. By failing to articulate adequate reasons to rebut the Declarations, the Examiner "failed to consider the totality of the record for the purpose of issuing a final rejection and thus erred as a matter of law." In re Alton, supra. It is trite law that the Examiner must consider the probative value of such evidence *vis-à-vis* any asserted *prima facie* case. See In re Oetiker, at 1445, 24 USPQ 2d at 1444. In re Keller, 642 F.2d 413, 208 USPQ 871, (CCPA 1981). In the absence of critical analysis, the Examiner appears to be relying solely upon her opinion rather than assessing weight to the objective evidence proffered in the Declarations. The Examiner, not being a skilled person in the medical art, must give weight to these expert opinions rather than substitute her own opinion. See In re Neave, 370 F.2d 961, 152 USPQ 274, (CCPA 1967).

A concise reading of the Declarations reveals that the experts relied solely upon the guidance and direction in the application's generic and specific disclosures pertaining to the claims coupled with their skills in the medical art in rendering their conclusions. Applicant, likewise, relies upon such disclosure.

As a final point, the Examiner's attention is again respectfully directed to the In re Wands decision, which led to the grant of a patent. The Court found that the PTO's determination of

nonenablement was unsupported by the evidence in the record. The Court further noted that the skill level in the art was high and that known materials were utilized in the practice of the invention in weighing the evidence. The instant fact situation is similar to that of In re Wands because the skill level is also high and known administration techniques and known materials are also utilized in the practice of the invention. In addition to such factual parallelism, Applicant provided expert objective evidence in the form of the Declarations of Drs. Finley, Wheeler, Lorincz, Heuser, and Meger. These medical experts read portions of the specification setting forth the generic invention and elected and non-elected species of such generic invention and determined that one skilled in the medical arts, armed with the guidance and direction in the specification disclosures, would be enabled to practice the methods defined in the claims and to predictably anticipate the results defined therein without need for resorting to undue experimentation. When the guidance and direction provided by Applicant's specification, the level of knowledge and the content of the prior at the time of the invention as established in the record, and Applicant's declaration evidence are interpreted in a reasonable manner, analysis considering the factors in In re Wands compels a conclusion that undue experimentation would not be required to practice the invention called for in the appealed claims.

From the foregoing remarks, Applicant submits that the instant application is in condition for allowance, and a Notice to such effect is respectfully requested. Should the Examiner have

any questions or require additional information or discussion to place the application in condition for allowance, a phone call to the undersigned attorney would be appreciated.

Respectfully submitted,

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